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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
17815

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Application Number	Filed
09/786,998	June 14, 2001

First Named Inventor
Maria Adele Pacciarini et al.

Art Unit	Examiner
1623	Ganapathy Krishnan

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☑ attorney or agent of record.
Registration number 32,608.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature

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April 4, 2012
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

The ensuing reasons support this Request for Review.

I. Background

This is the second Pre-Appeal Brief Request for Review in this case. The first (March 28, 2011) was resolved in Applicants favor; Notice of Panel Decision, April 8, 2011; prosecution was re-opened and the instant rejection imposed, and made final (January 9, 2012).

The instant rejection, *infra*, is the same rejection based on the same art as imposed two years ago; see Official Action, January 28, 2010, page 5. That rejection was expressly withdrawn (see Official Action, May 10, 2010, page 3, ¶7) given Applicants' response (April 28, 2010). The claims then are substantially the same as the claims now. The present Official Action gives no justification for resuscitating a rejection overcome long ago. This case has now been in prosecution for over ten years.

II. The Rejection

Claims 18, 20-23, 26, 27, 29, 30 and 34-42 pending. All are finally rejected under 35 U.S.C. §103 per Official Action of January 9, 2012.

The primary reference is Bargiotti et al. U.S. 5304687.

The secondary references are: Kuhl et al. (*Cancer Chemother. Pharmacol.*, 1993, 33, 10-16), Nakamura et al. (*Gan. To Kagaku Ryoho* 1988, Aug 15 (8 Pt2), 2562-7, English Abstract), Gorbunova (*Intrahepatic Arterial Infusion...Liver*, 1990), and Brem et al. (U.S. 5626862).

III. The Invention

The claims are to a method of treating a human liver cancer. The method entails intrahepatic administration of methoxymorpholino doxorubicin (MMDX) in a specified dosage. Other claims are to a pharmaceutical composition for treatment of human liver cancer via intrahepatic administration comprising MMDX sufficient for the dosages recited. The invention requires a surprisingly reduced dosage, as heretofore with other actives, and dramatically lessens toxic side effects normally associated with liver cancer treatment.

IV. Clear Error

The rejection is improper for failure to show proper motivation. The primary reference is silent as to using MMDX for liver cancer; silent as to selectivity to liver cancer; silent as to intrahepatic administration; and silent as to the surprisingly low dosages claimed.

The only secondary reference to mention MMDX (Kuhl et al.) is also silent for liver cancer, liver selectivity, intrahepatic administration, and the low dosages claimed. The remaining secondary references are to a different active altogether, i.e., adriamycin, otherwise known as doxorubicin (hereinafter ADM). Notably, one of the secondary references (Gorbunova) reports not only a level of toxicity for ADM that motivates away from the inventive improvement with MMDX in this side effect, it actively dissuades one from MMDX by also reporting that certain patients with liver cancer had no response to ADM.

V. Discussion

A. The Claims

Of Claims 18, 20-23, 26, 27, 29, 30 and 34-42, the following are independent: 18, 34 and 40. Commonly, Claims 18 and 40 are to a method of treating human liver cancer using MMDX via intrahepatic administration in a dose ranging from about 100mcg/m^2 to about 1000mcg/m^2. Claim 40 further specifies the administration is via the hepatic artery and that the administration is an infusion of from about 15 minutes to about 30 minutes every 4 weeks. These features appear in various dependent claims.

Claim 34 is to a pharmaceutical composition for the treatment of a human liver cancer by intrahepatic administration via injection into the hepatic artery. The composition comprises MMDX in an amount sufficient to provide a dosage of about 100 mcg/m2 to about 1000 mcg/m2; and a pharmaceutically acceptable agent which remains selectively in a liver tumor after injection, *e.g.* an iodized oil.

The specification reports the unusually high potency of MMDX versus ADM (application, page 1, line 26 to page 2, line 1) and the significantly high activity of MMDX in models where there is ADM resistance (page 2, lines 5-8). Hematological toxicity in clinical studies for the invention showing Grade 1 leucopenia (the mildest grade measure for chemotherapeutic toxicity) are at

page 11, line 27 to page 12 line 3. Non-hematological toxicity is at page 12, showing Grade 1 and Grade 2 leucopenia, both of which are at the low end of the toxic spectrum.

B. The Primary Reference: Bargiotti et al.

The Official Action states that Bargiotti et al. shows that MMDX inhibits "human carcinoma" and that the only element missing is intrahepatic administration. (Official Action, January 9, 2012, page 4, 1st ¶).

This is erroneous. The only human data in Bargiotti et al. for MMDX are to "mammary human carcinoma." See Table 6 therein, compound A4. This is not a blanket teaching to "human carcinoma" as officially alleged, let alone liver cancer, as claimed. And it is error to so interpret Bargiotti et al. Indeed, the rules of examination preclude stretching a limited teaching to mammary cancer to all human cancers, including liver cancer, see e.g. MPEP 2107.03. The Official Action concedes Bargiotti et al. does not disclose intrahepatic administration. But it also does not disclose the dosages claimed. Nor does not disclose benefits, such as amelioration of toxicity, associated with the foregoing and the invention in liver cancer.

Thus, contrary to the official position of there being only one difference between Bargiotti et al. and the invention, there are numerous and meaningful differences.

There is no proper, objective motive to provide or foresee any of these missing elements from the secondary references.

C. The Secondary References:

Kuhl et al.: This is the only ancillary reference to mention MMDX. But Kuhl et al. does not disclose use for liver cancer. And for the reasons above, use of MMDX in human leukemia and lymphoma cell lines does not properly, on its own, suggest successful use in liver cancer. Kuhl et al. discusses potent metabolite formation of MMDX in the liver. But this self-evidently has nothing to do with treatment of liver cancer. It certainly does not presage it. To the contrary, one would be far more likely to wonder if a diseased liver, e.g. one having cancer, the subject of the invention, would still be able to metabolize as stated in Kuhl et al., thus rendering use of MMDX for this purpose wholly problematic and without any reasonable prediction of success.

Nakumura et al.: Teaches ADM, not MMDX. Reference is made to the distinction between ADM and MMDX in the specification as indicated *supra*. Additionally, Nakumura at el.

explicitly informs the reader that there is no correlation between the amount of ADM (dosage) and the change in total bilirubin (ΔT-bil), the marker to evaluate ADM on the liver. See Nakumura et al., Section III, Results. No correlation with dose and ADM perforce means there is no correlation, from Nakumura et al. with dose and MMDX —dosage being an element of the claims, and surprisingly low at that— let alone effectiveness of MMDX, still let alone the surprising advantages described *supra* in using MMDX for liver cancer. None of this is found in Nakumura et al. Morever, Nakumura et al. cannot be read in isolation. It must be read in conjuction with Gorbonova, *infra*, also directed to ADM, and published after Nakumura et al.

Gorbunova: Is directed to ADM, not MMDX. Gorbunova not only does not predict the invention, but it actively teaches away from it:

First, Gorbunova reports toxicity for ADM up to level of Grade II-IV leucopenia for 50% of patients (3rd page, 4th paragraph "Regarding the toxicity…"). Compare this with the Grade 1 leucopenia resulting with the invention, *supra*. Additionally, one reading Gorbunova would not employ MMDX at the low dosages claimed, but would instead be clearly inclined to employ increased dosages: see "Finding 2" (Gorbunova, last page) whereat it approvingly relates the "possibility of increasing the total dosage and lengthening the time of intra-arterial infusion." This increase in dosage is in direct contrast to the dosages Applicants have discovered and claimed with MMDX.

Second, Gorbunova reports "no objective responses" in a group of twelve patients with a primary inoperable hepatic carcinoma who received 17 courses of 72-hour adriamycin infusions (2nd page, 4th paragraph from bottom). This is in stark contrast to the efficacy of the invention, where there is not only a clinical response, but one that is far superior and unexpected. For example, two objective tumor responses were observed at 200 mg/m^2 (see instant specificaion page 13, lines 9-10). This translates into a reduction of the initial tumor mass of at least 50%. Indeed, one patient evinced a complete response (Page 13, lines 14-17) from the practice of the invention. None of this is suggested by Gorbunova.

Brem et al.: This is cited for general teachings on pulse and short term administration of chemotherapeutic agents. It does not relate to liver cancer or MMDX and is at a farther remove than the other secondary references.

See also Amendment and Remarks Under 37 C.F.R. §1.114, April 28, 2010.

VI. Conclusion

The flaws in the rejection thus crystallize: Bargiotti et al. does not teach MMDX for liver cancer, or intrahepatic administration, or the dosages claimed, or the advantages attained.

Kuhl et al. suffers the same deficiencies, but now also raises a serious question as to whether a cancerous liver would provide the same metabolic actives for MMDX as otherwise touted in Kuhl et al. This question, in essence, draws Kuhl et al. back from the use of MMDX in liver cancer. It certainly raises grave issues as to predictability of success, as required under §103.

Nakumura et al. is directed to ADM, not MMDX, and its self-admitted lack of correlation for dose between ADM and liver marker efficacy leaves one without guidance for MMDX or the other elements claimed. Indeed, Nakumura et al. has to be read in concert with Gorbunova (which is later in time).

Gorbunova, like Nakumura et al. uses ADM, not MMDX. But Gorbunova teaches away from the invention and its advantages: it reports high levels of toxicity and a cohort of non-responsive liver cancer patients. This teaching away pervades all the teachings of record whether they be for MMDX or ADM. When combined with the other art, as in the rejection, one must account for Gorbunova's dismal reports of poison and failure. One is not motivated by any fair and objective to envision successful use of MMDX, still use of MMDX leading to the benefits that accrue with the invention.

Applicants submit that the claims are non-obvious and patentable in all respects. Favorable reconsideration and withdrawal of the rejection and passage to allowance of the instant application is requested.

Respectfully submitted,

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